CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-225

MEDICAL REVIEW

Medical Officer's Review of NDA 21-225

Sponsor:	Berlex Laboratories, Inc.
Drug Name:	Mirena® (levonorgestrel-releasing intrauterine system)
NDA number:	21-225
Pharmacological category:	progestin-releasing intrauterine device (IUD)
Route of Administration:	intrauterine
Dosage:	52 mg released at a rate of 20ug/day
Indication:	prevention of pregnancy
Comment:	see chemistry, pharmacology, and biopharmaceutical review
Related Products:	ParaGard® T 380A Intrauterine Copper Contraceptive, Progestasert®, oral contraceptives, Plan B™ tablets and Norplant System

Date Submitted:	February 2, 2000
Date Received by Medical Officer:	February 8, 2000
Date Review Completed:	December 5, 2000

Mirena® Executive Summary

I. Recommendations

The data presented in this NDA support the safety and effectiveness of Mirena for up to 5 years of continuous use. Marketing approval in the USA is recommended.

It is further recommended that Berlex Laboratories, Inc. (Berlex)

- follow the usual post-approval reporting requirements. In particular Berlex must submit the final report of study LE102-96502 in 2001 that will include data on insertion complications resulting in hospitalization. Study LE102-96502 was a large postmarketing study of 26,000 users in Finland that evaluated length of use, safety and efficacy of Mirena.

- follow up adverse event reports related to pregnancy for as much outcome information as possible. Pregnancy reports must be followed up for birth defects, septic abortions, premature deliveries, and duration of the exposure to Mirena whenever this information can be obtained.

- provide a separate section in the periodic safety update reports for USA adverse event data and estimates of exposure to Mirena. Intrauterine devices (IUDs) are not widely used in the USA and it is possible that lack of experience will adversely affect the safety profile of Mirena. For example, perforations may be a greater problem in the USA than elsewhere.

II. Summary of Clinical Findings

Clinical Program Overview:

Mirena is a medicated intrauterine device (IUD) containing 52 mg of levonorgestrel released at a rate of 20 ug/day. Berlex presented 3 phase III contraception trials that took place in Finland and Sweden from 1982 to 1996. The total overall exposure to Mirena was 64,136 woman-months. Six hundred thirty-three women completed 5 years of use.

Efficacy:

The efficacy of Mirena was demonstrated by a one-year Pearl Index of 0.19 pregnancies per 100 woman-years. The five-year Pearl Index was 0.08 pregnancies per 100 woman-years. These Pearl Indexes were calculated from 1169 women who were between 18 and 35 years old at baseline.

The reported pregnancy rate may not predict effectiveness with typical use because of limitations in the clinical studies. For example, routine pregnancy testing was not done at

the end of the studies or on patient withdrawal from the study. In addition, approximately 6% of women were lost to follow-up in the largest efficacy trial. More than 75% of the women in the two largest trials had used IUDs previously. (Information on prior IUD use was not collected for the third trial.) Presumably women who had experienced IUD problems in the past would be less likely to volunteer for an IUD trial, possibly confounding the results with a bias for improved safety and efficacy.

For comparison, the published "perfect use" Pearl rate for the
- birth control pill is 0.1
- diaphragm is 6
- male condom is 6
- copper T 380A IUD is 0.6
- use of no contraception is 85

Safety:

There were no deaths related to Mirena use.

Serious side effects include

- PID. There were sixty-five women in the 3 contraception trials diagnosed with PID, for a rate of 1 per 100 women-years. For comparison, 1980 annual incidence estimates of PID in modern industrialized countries were 1-1.3 per 100 women (*Am J Obstet Gynecol* 1980; 138:880-92).

- Group A streptococcal sepsis. There have been 4 spontaneous postmarketing reports of group A streptococcal sepsis as of 1999. In all 4 cases, symptoms started within hours of insertion. There were no cases in the three controlled contraception trials. Group A streptococcal sepsis has also been reported postpartum and in association with minor surgical procedures. Though rare, the problem is serious enough to be included as a warning on the label.

- Ovarian cysts. Ovarian cysts seem to occur with higher frequency in some of the supportive studies than in the general population. However, most cysts are not clinically significant. In addition, the incidence of ovarian cysts depends on how much effort is made to find them. For example, one study that was specifically designed to detect ovarian cysts by daily ultrasound showed cyst formation in 42% of 26 ovulatory cycles in women who had used the levonorgestrel IUD for more than 7 years. However, there were only 8 ovarian cysts listed as serious adverse events in the 3 pivotal contraception trials, or 148/100,000 woman years. For comparison, the reported annual incidence of ovarian cyst requiring hospitalization in the USA for the years 1988-1990 was 327/100,000 women.

- Ectopic pregnancy. The Pearl index for ectopic pregnancies in the pivotal studies in women 35 and younger was 0.097 (95% C.I.= 0.0, 0.544) per hundred women-years.

The population Pearl index chosen by the sponsor as a historical control was 1.2-1.6 ectopic pregnancies per 100 women-years among sexually active women using no contraception (Lindblom B, Thorburn J. Spiralgraviditet. *Lakartidningen* 11:923-4 1988). However, women at increased risk for ectopic pregnancy (for example, women with a history of ectopic pregnancy or a recent history of PID) were excluded from the pivotal trials. In addition, as many as half of pregnancies that do occur are ectopic. For example, 5 of 10 pregnancies in the 2 large contraception trials and 65 of 108 pregnancies in the postmarketing reports and surveillance were ectopic.

Reviewer comment: Labeling must include warnings that Mirena may not protect against ectopic pregnancy and ectopic must be ruled out if pregnancy occurs.

- Myocardial infarction. There was one myocardial infarction in the 3 pivotal trials. It occurred after 6 years of Mirena use in a 42-year-old woman with pre-existing hypertension who was on antihypertensives.

Common, but less serious side effects, include

- Expulsions. Expulsions occurred in 97 of 2339 women in the 3 controlled studies. Seventy expulsions occurred in the first year of use. The overall discontinuation rate for expulsion was 3.21 per 100 women at 1 year and 5.21 per 100 women over 5 years (by Kaplan-Meier calculations). For comparison, discontinuation for expulsion for the ParaGard T 380 A IUD is 5.7 per 100 users in the first year of use, according to its labeling.

Reviewer comment: Expulsions appear to be more frequent in the first year of use of Mirena.

- Menstrual irregularity. Menstrual irregularity was common with Mirena and affected continuation rates. Bleeding patterns were evaluated in 4 contraception studies and 3 published reports. The bleeding results in study AV97 (section 5.10.4) are typical of these reports: The median number of bleeding /spotting days in the first 84-day period were 10 bleeding days and 20 spotting days. However, this declined to 0 bleeding days and 7 spotting days in the fourth 84-day period. The percentage of women with amenorrhea in first 84-day period was 1% but increased to 21% in the fourth 84-day period. Overall, in the three controlled contraception trials, the cumulative discontinuation rate by Kaplan-Meier for all bleeding irregularities was 16 per 100 women-years at 5 years.

Other safety issues and pertinent negative findings include

- There were no deep vein thromboses or pulmonary emboli in the 3 trials.

- Fetal safety. Fetal safety data are limited. No pattern of birth defects emerges from 35 exposed pregnancies in which infant outcome data are available from postmarketing reports.

- Perforation. There were no perforations in 2339 attempted insertions. However, perforation is a serious potential risk of any IUD.

- Weight changes. There was no difference in weight at baseline and at 1 year between women using Mirena and women using a birth control pill in study AV97. There was also no difference in mean weight change over 5 years between women using Mirena and women using a copper IUD.

- Blood pressure. There were no clinically significant changes in blood pressure in the 3 pivotal studies, although 2 of the 3 studies showed statistically significant decreases and 1 of the 3 showed a statistically significant increase with time.

- Hemoglobin. In general mean hemoglobin concentrations tended to increase with time. For example, there was a statistically significant increase from 135.8 to 136.2 g/L over 5 years in study AY99 (section 3). However, the clinical significance of a 0.4g/L increase is unclear. In addition, the rise in hemoglobin may be partly or wholly explained by dropouts who may have had low hemoglobin concentrations. For example, in study AY99, only 47% of the women who started in the study were still in the study at 5 years, and 10% had discontinued because of bleeding problems.

- Lipids and glucose. The sponsor presents no data on lipids or glucose in women using Mirena for birth control. Limited data on lipids comes from studies in women using Mirena as the progestin part of a hormone replacement therapy (HRT) regimen, and are thus confounded by the concomitant use of estrogen. No adverse lipid effects were seen in these studies. Systemic levonorgestrel levels are lower in Mirena users than in users of other levonorgestrel birth control products, and therefore systemic effects from levonorgestrel are expected to be no greater with Mirena than with other levonorgestrel-containing birth control products.

- Bone density. The sponsor presents no data on bone density. However, there is literature support for no adverse effect on bone density from Norplant implants, which produce somewhat higher systemic levels of levonorgestrel.

- Cervical cytology. Abnormal cervical cytology in Mirena users does not appear to be different from that seen in sexually active women.

- Breast cancer. The incidence of breast cancer in Mirena users in these studies is no higher than the expected incidence in women of reproductive age. There were 4 breast cancers in 5371 woman-years in the 3 controlled contraception trials, or 74/100,000 woman-years. The 4 women ranged in age from 36 to 44, and had used the levonorgestrel IUD from 3 to 6 years. For comparison, the incidence of breast

—cancer among women aged 35-44 years in Finland between 1977-1981 varied between 40 and 74 per 100,000 women per year.

Drug-drug interactions were not studied but are not expected to play a major role in the effectiveness or safety of Mirena. Unlike other contraceptive methods containing levonorgestrel, the effectiveness of Mirena appears to depend more on the local than the serum concentration of levonorgestrel. In fact, the serum concentration of levonorgestrel produced by Mirena is lower than the serum concentration produced by any currently marketed levonorgestrel-containing contraceptive in the USA (e.g., approximately one tenth the serum concentration produced by an oral contraceptive containing 0.1mg levonorgestrel and about half that produced by the Norplant System®).

Recommended warnings include the warnings that are currently on the USA labels for the other two USA-approved IUDs. These include warnings about pelvic infection, ectopic pregnancy, congenital anomalies, septic abortion, perforation, embedment, and breast cancer. The section on pelvic infection includes a discussion of group A streptococcal sepsis. In addition, warnings related to the progestin component of Mirena include a warning about ovarian cysts and a warning about potential glucose tolerance changes. And finally there will be a warning about irregular bleeding and amenorrhea that is specific to this IUD.

The exact risk of pregnancy to a woman and her fetus with Mirena in place is not known because there were so few pregnancies reported in the pivotal trials.

Dosing:

Levonorgestrel is a progestin found in a variety of approved contraceptive products, and the systemic concentration of levonorgestrel produced by Mirena is approximately 10% of that produced by an oral contraceptive containing 0.1 mg of levonorgestrel. The local endometrial concentrations of levonorgestrel, however, are over 100 times higher in Mirena users than in users of oral contraceptive containing 0.25 mg levonorgestrel. Therefore, local tissue effects were studied. Two studies involving a total of 74 women evaluated endometrial effects of the Mirena, and found endometrial atrophy, decidualization and inflammation. In addition 13 studies are presented in which Mirena was used as the progestin component of hormone replacement therapy. Approximately 540 women had endometrial biopsies and none had atypical endometrial hyperplasia or cancer. One woman had simple cystic hyperplasia.

Special Populations:

Gender effects do not apply to Mirena since it is only indicated in women. The pivotal studies were conducted in Sweden and Finland and did not address ethnic/racial differences. There are no issues with the elderly as the only indication sought is pregnancy prevention. Mirena was not studied in women with liver disease and is contraindicated in women with liver disease. It was not studied in women with renal

impairment in this submission. There were no pediatric studies and no plan to do *pediatric studies was presented.* *However, since Mirena is recommended for parous* women in stable, monogamous relationships, it is unlikely to be used in the pediatric population. Mirena is contraindicated in pregnancy.

Table of Contents

1.0 RESUME

This review summarizes and analyzes the clinical data submitted by Berlex Laboratories, Inc. (Berlex) supporting a new drug application for Mirena, a levonorgestrel-releasing intrauterine device (IUD).

The purpose of the analysis is to determine the safety and effectiveness of Mirena as a contraceptive method.

Berlex provides 207 volumes of clinical data, including data from 3 large clinical trials submitted as the pivotal trials. This review analyzes each of these trials individually. Berlex also provides 25 other clinical study reports, numerous publications, and 5 volumes relating to clinical pharmacology studies. All studies were done outside the USA except for a Population Council phase 3 multinational study. Berlex submits publications only for this study.

The review summarizes the data and gives recommendations regarding approval and labeling based on the clinical data and an independent review of the literature.

2.0 BACKGROUND

2.1 Regulatory history

The levonorgestrel IUD was developed in Finland in the 1970's. Leiras Oy of Finland sponsored the first large-scale phase 3 trial in Europe and enrolled patients from 1982-1989.

The FDA received its first submission regarding the levonorgestrel IUD from the Population Council on August 31, 1983. In IND ⌐▬▬the Population Council proposed to compare the levonorgestrel IUD with the TCu380Ag IUD in 200 women in California. The study was part of a larger multinational study of the levonorgestrel IUD also sponsored by the Population Council. The FDA requested additional carcinogenicity, toxicity and teratogenicity studies. The study was allowed to proceed with a deficiency letter issued by the FDA regarding manufacturing and chemistry issues. Clinical issues were primarily related to informed consent, especially with regard to amenorrhea and unknown toxicity to the fetus.

The Population Council next came to the FDA in 1991 for a pre-NDA meeting along with Leiras Oy. ⌐▬▬ ; had discontinued production of the polymer used to make the hormone matrix and they needed to substitute a new polymer. The sponsor proposed a one-year study to compare the IUD using the new polymer (containing 52 mg levonorgestrel) with the IUD using the old polymer (containing ▬▬ levonorgestrel) using comparative blood level data and in vitro release data. The agency required comparative in vivo/ in vitro release rates.

Another pre-NDA meeting was held on January 27, 1998 with Berlex. Berlex was in the process of obtaining the IND from the Population Council. The IUD had undergone another formulation change due to change in the polymer manufacturer. The main pharmacokinetic issues were the *in vivo/in vitro* correlation of the studied device with the to-be marketed device (both containing 52 mg levonorgestrel). The main clinical issues centered on using studies that documented patient consent and had auditable data. On March 6, 1998, the agency received official notice of the sponsorship transfer from the Population Council to Berlex.

On March 10, 1999 Berlex and the agency had a teleconference centering on issues related to the formulation changes and the data needed to confirm *in vivo/in vitro* correlation between the device used in the clinical studies and the to-be-marketed device (both containing 52 mg levonorgestrel).

On July 19, 1999 Berlex and the FDA held another teleconference to discuss a pre-NDA packet submitted in April 1999. Again the issues of informed consent and auditable data were raised. The FDA required at least 200 women who completed 5 years of product use at valid sites, at least 35,000-40,000 women-months of data, and clarification of the number of patients at valid sites. Valid sites were defined as only those sites with verifiable informed consent and auditable data.

On August 10, 1999, Berlex and FDA had a teleconference to discuss *in vivo/in vitro* correlation of the to-be-marketed levonorgestrel IUD to the studied levonorgestrel IUD. They decided that Berlex would submit additional data during the review clock to validate the *in vivo/ in vitro* correlation.

2.2 Clinical background and proposed mechanism of action:

This section describes Mirena, compares it to related products, and discusses the proposed mechanism of action.

Mirena is a T-shaped IUD that contains 52 mg of levonorgestrel in a sleeve on the stem of the T. Levonorgestrel is slowly released from the sleeve into the uterine cavity for 5 years. Levonorgestrel is a familiar drug used in approved contraceptives. However, Mirena is unique among levonorgestrel contraceptives because the contraceptive action is more likely related to high local concentrations of levonorgestrel in the uterus, rather than serum concentrations of levonorgestrel.

IUDs currently approved in the U.S. are the ParaGard® T 380A IUD, a copper-containing IUD providing 10 years of contraception, and the Progestasert®, a progesterone-containing IUD providing 1 year of contraception.

A potential advantage of Mirena over the copper IUD is less menstrual blood loss. A potential advantage over the currently marketed progesterone IUD is the 5-year period of effectiveness.

Potential disadvantages of adding levonorgestrel to an IUD include systemic and local adverse effects. Since the drug itself has been approved and marketed in several oral contraceptives and a subdermal implant, the systemic adverse effects are well characterized. However, it has not previously been approved in this country for intrauterine delivery. A potential disadvantage related to intrauterine delivery includes adverse effects of high local concentrations of levonorgestrel on nearby tissues or a fetus.

The mechanisms of action of IUDs are still largely unknown. Mirena has progestational effects on cervical mucus, tubal motility and endometrial histology, which all may contribute to contraceptive efficacy. At least one study suggests that the levonorgestrel IUD exerts its effect before implantation. However, which (if any) of these mechanisms is most important is not known.

2.3 International marketing experience

As of September 27, 1999, the levonorgestrel IUD was registered and marketed in 28 countries under the names Mirena and Levonova, and approved but not yet marketed in 14 additional countries.

Berlex submitted a Periodic Safety Update Report (PSUR) during the course of the review covering the period of September 28, 1999 through March 27, 2000. As of March 27, 2000, Mirena had been granted a marketing authorization in 52 countries and Berlex estimated that there were over ⎯⎯ ' current users of Mirena (based on cumulative sales volumes and assuming a yearly discontinuation rate of 10%). There have been no market withdrawals.

2.4 Pharmacology, pharmacokinetics and pharmacodynamics

This section summarizes key pharmacologic, pharmacodynamic and pharmacokinetic findings from the data submitted by the sponsor.

Animal studies revealed no adverse findings. There was no genotoxicity with the levonorgestrel IUD or its components *in vitro* or *in vivo*. There was no toxicity in rats implanted for 6 months or cynomolgus monkeys implanted for 9 months. There was no embryo or maternal toxicity in pregnant rabbits with a bioequivalent levonorgestrel IUD. The reader may consult the pharmacology review for more details.

In women using Mirena, mean serum concentrations are roughly half of those seen with the Norplant system, and roughly one tenth of those seen for an oral contraceptive containing 0.1 mg levonorgestrel. Median serum levonorgestrel concentrations over a 5-year period are approximately 100 to 200 pg/ml (see section 4, Table 5). Unlike other products containing levonorgestrel, Mirena is thought to act mainly via its direct local effects on the uterus, rather than through serum concentrations of levonorgestrel.

12

The local levonorgestrel concentrations are quite different from the concentrations seen with other levonorgestrel-approved products. Therefore, adequate studies of local effects are important. Based on a tissue study of 9 women undergoing hysterectomy who received a Mirena prototype (̄ ̄ ̄ ̄ 36-49 days before surgery, endometrial concentrations of levonorgestrel were over 100 times higher in levonorgestrel IUD users compared to users of a 0.25-mg levonorgestrel pill. The high local concentration dropped off rapidly, with the Fallopian tube epithelium concentrations roughly equal between levonorgestrel IUD users and users of a 0.25 mg pill. The sponsor presents studies of the local effects on the cervix and the endometrium, which are reviewed in section 6. The studies did not show any malignant changes in these tissues.

Another concern with high local levels is fetal exposure. There is no information about fetal effects from the phase 3 trials because there were so few pregnancies and none that continued beyond the first trimester. However, the sponsor includes postmarketing safety update reports that includes pregnancy information, presented in Section 7.0.

Information on mechanism of action of the levonorgestrel IUD is limited. One study showed a decrease in cervical mucus weight after levonorgestrel IUD insertion. In another study investigators followed 19 levonorgestrel IUD (a ──── prototype) users through 1 cycle and looked for signs of early implantation by testing for serum levels of human chorionic gonadotropin (HCG) 0-3 days before menses was expected. No HCG was detected in any of the levonorgestrel IUD subjects. In contrast, 7 of 22 non-contracepting women, 8 of 40 Lippes loop users, and 2 of 41 copper IUD (Nova T) users had HCG production. Only cycles that were ovulatory based on cervical mucus and biphasic basal body temperature changes were included in this small study. In addition, if menstruation did not occur and pregnancy ensued, the case was discarded (five women in the non-contracepting group and one in the Lippes loop group). These results suggest that disruption of an implanted embryo is not a mechanism of levonorgestrel IUD action since HCG production is first detectable around the time of implantation.

Three studies are presented as dose-finding studies. One study compared the Nova T (N=30) to a levonorgestrel IUD (N=30) releasing 10 ug/day of levonorgestrel. The women were followed for 1 year. There was 1 pregnancy that occurred in the levonorgestrel IUD group at 7 months. The pregnancy occurred in a woman with the lowest serum levels of levonorgestrel (13pg/ml), and investigators suspected a faulty device. Another study compared a levonorgestrel IUD releasing 20 ug/day levonorgestrel with a levonorgestrel IUD releasing 30 ug/day levonorgestrel. Women were followed for 2 years. There was 1 pregnancy in the levonorgestrel IUD-20 group (in the first year) and none in the levonorgestrel-30 group. The difference in pregnancy rates did not reach statistical significance. The third study compared a 30 ug/day levonorgestrel IUD to a 10ug/day levonorgestrel IUD. There were no pregnancies. However, the IUDs were inserted in postpartum, breastfeeding women.

The studies presented do not address demographic effects on PK/PD.

The small number of pregnancies with outcome information precludes any conclusions about a lack of adverse fetal effects.

Although the sponsor believes that the mechanism of action is local, low systemic concentrations of levonorgestrel are produced and some systemic contribution is not ruled out by these studies. Therefore, there is a possibility of drug-drug interactions.

Dose-finding studies were limited. It appears that no more than 20 ug/day is needed for contraception, but the lower limit of effectiveness is unclear. Although there was 1 pregnancy in 30 women in the 10/ug/day group, it is possible that there was a problem with the inserted device. The third study presented as a dose-finding study gives no information about effectiveness since the women were at low risk for pregnancy (postpartum, breastfeeding).

3.0   STUDY AY99

The reevaluation study

3.1 Objectives

The objective of this study was to reanalyze the safety and efficacy of the levonorgestrel IUD in women who participated in a large, multicenter study comparing the clinical performance and contraceptive efficacy of Nova T (a copper IUD) with that of the levonorgestrel IUD. The reason for the reanalysis was to focus on the subset of study sites called qualified sites for which source data and informed consent were verifiable. Only the levonorgestrel IUD data was reanalyzed.

Reviewer's comments:

Unless otherwise stated, the data presented in this section comes from the qualified sites. Where informative, some data from unqualified sites and from the original study copper IUD arm is presented but is not relied on for safety and efficacy assessments.

3.2 Design

The original study was an open, phase 3, randomized study comparing the levonorgestrel IUD to the copper IUD in a ratio of 2:1. Investigators enrolled 2758 women from 1982 through 1985. There were 15 centers in 6 countries (Denmark, Finland, Norway, Sweden, Hungary and the United Kingdom.) The women were followed for 5 years. The levonorgestrel IUD used was a prototype of Mirena, containing ——— of levonorgestrel. Like Mirena, the release rate of levonorgestrel was 20 ug/day. 1821 levonorgestrel IUD users were enrolled in the original study.

The reevaluation study analyzed results from 1855 women and included only levonorgestrel IUD users. The number of women analyzed (1855) differs from the number analyzed in the original study (1821) because the reevaluation report includes one additional center and because women who had unsuccessful insertions were included in the reevaluation, as well as women who were recruited although they did not fulfill the inclusion criteria.

Eight of the 15 sites were unqualified because of missing source data or informed consent documentation. The unqualified centers had 745 levonorgestrel IUD users. Seven centers were qualified. The qualified centers had 1110 levonorgestrel IUD users. The qualified centers were all in Finland or Sweden. The data was analyzed for both the qualified and unqualified centers to look for any differences. A total of 523 patients completed 5 years of levonorgestrel IUD use at the qualified centers.

Women were evaluated before insertion, and at 3, 12, 24, 36, 48, and 60 months. Hemoglobin was measured at every visit and cervical smears were done before insertion and yearly thereafter. There was no routine pregnancy testing, but women had a pelvic exam at each visit. Investigators could not verify bleeding and spotting data against source documents so this data was not reevaluated. Iron was the only treatment allowed for bleeding irregularities.

The protocol of the original study recommended urinary pregnancy testing if pregnancy was suspected. In particular pregnancy testing was recommended if menses were delayed by 2 or more weeks, and repeated if there was no menstruation for 6 full weeks. At each follow-up visit women were asked if they were pregnant and urinary testing was recommended if they were uncertain. There was no routine pregnancy testing if the woman had her IUD removed during the study. There were no requirements for regular cycles, although women were required to have at least one prior pregnancy and be within 10 days of a menstrual period to have an IUD inserted. Contraceptive methods other than the IUD were not to be used concomitantly. Continuous progestin treatment (defined as more than one cycle of treatment) for reasons other than contraception was also not allowed.

3.3 Study population

At qualified centers, the average age was 31 years with a range of 18-38. Seven women had no previous pregnancies. Seventy five percent had used an IUD before. The mean (SD) cycle length was 28.3(2.5) days, the median (Q1, Q3) cycle length was 32(28-35) days, and the range of cycle lengths was 14-70 days.

3.4 Inclusion and exclusion criteria

Inclusion Criteria:

- Subjects informed of the purposes of the study and of risks to health and pregnancy and who had given their oral informed consent
- Willingness to rely solely on the levonorgestrel IUD as the contraceptive method.
- Willingness to return to the center for regularly scheduled visits and be accessi'le for regular follow up visits
- Willingness to accept an induced abortion in case of accidental pregnancy
- Must be within 3 to 10 days of the onset of menstrual bleeding, but not later than 5 days from the last day of menses, or immediately after a first trimester abortion performed by vacuum aspiration
- Age 18 –38
- Regularly exposed to the risk of pregnancy

Exclusion criteria:

- History of current clinical evidence of endocarditis
- History of cancer of any kind
- Copper allergy or Wilson's disease
- PID or salpingitis during the last 12 months
- Acute cervicitis or vaginitis
- History of ectopic pregnancy
- Persistent abnormal genital bleeding
- Anemia
- Diabetes
- Pathological galactorrhea
- Severe hirsutism
- Jaundice
- Mental illness, depression
- Congenital or other abnormality of uterus
- Currently pregnant or breast feeding
- Use of injectable steroid hormones for contraception during 12 preceding months.

3.5 Screening period (for the original study)

Women had a general physical exam, pelvic exam, hemoglobin, and Papanicolaou (PAP) smear and were instructed to keep a menstrual diary.

3.6 Treatment period (for the original study)

Women were seen at 3, 12, 24, 36, 48, and 60 months. PAP smears were done yearly. Hemoglobin, general physical exam and pelvic exam were done at each visit. Bleeding diaries were assessed.

3.7 Statistical procedures

Analyses were done on the intent-to-treat population. Pregnancy rates were calculated using Pearl index and Kaplan-Meier estimates. Discontinuation rates were calculated by Kaplan-Meier estimates with 95% confidence intervals.

3.8 Withdrawals and compliance

The number of lost-to-follow-up patients is not given; however, the lost-to-follow-up patients are included in the "other personal" reasons for discontinuation (7.88 per 100 women at 5 years, section 3.9, Table 2).

One patient was excluded from the efficacy analysis because she refused to start treatment after randomization. In 11 subjects the insertion of the levonorgestrel IUD failed. One subject discontinued because the investigator removed the levonorgestrel IUD by accident after a successful insertion.

Discontinuation rates for various reasons were analyzed as secondary efficacy variables and are discussed further in the following section.

There were numerous minor protocol deviations, but the deviations that may have had a small effect on efficacy calculations were 3 women who were sterilized but continued the IUD, and 9 women who used other contraceptives.

3.9 Efficacy analysis

3.9.1 Pregnancy rates

The primary efficacy variable was pregnancy. The pregnancy analysis follows.

In the qualified centers:

Two levonorgestrel IUD users became pregnant. The first woman had an intrauterine pregnancy conceived 2 years after device insertion. The pregnancy was diagnosed by clinical judgment, pregnancy test and ultrasound. The levonorgestrel IUD was in place, and she had an induced abortion at 9 weeks gestation. The investigator felt that a uterine myoma caused the failure because a 4.3x3.2x3.7 cm myoma was seen on ultrasound. (She had had the diagnosis of uterine myoma 7 years before IUD insertion but no note was made of uterine enlargement by investigators at admission or during the study.) The second woman became pregnant 10 months after the device insertion. The pregnancy was diagnosed by pregnancy test. This woman also had an induced abortion at 8 weeks gestation. The investigator felt that device expulsion caused the failure because the device was not found at the time of abortion.

The first year Pearl index based on 884 women from the qualified centers who were 35 *years old or younger at baseline and 9225 28-day cycles is 0.13* pregnancies per 100 women-years.

In the unqualified centers:

Five women became pregnant. Two pregnancies were ectopic, and 3 were intrauterine. All were terminated. Both ectopic pregnancies occurred with the IUD in place. One intrauterine pregnancy terminated with a spontaneous abortion at 8 weeks gestation and was felt to be secondary to IUD expulsion. Another intrauterine pregnancy terminated with a spontaneous abortion at 7 weeks gestation with the IUD in place. A possible reason for contraceptive failure was not recorded. The third intrauterine pregnancy was terminated with an elective abortion with the IUD in place. The history of this pregnancy was obtained 8 years after the patient's last study visit and gestational age was unknown. Two pregnancies occurred 3 years post insertion and 2 occurred 4 years post insertion. The time of insertion of the fifth was not recorded.

The first year Pearl index based on 663 women from the unqualified centers who were 35 years old or younger at baseline and 6743 cycles is 0.18 pregnancies per 100 women-years.

3.9.2 Continuation rates and discontinuation rates for various reasons

The secondary efficacy variables were continuation and discontinuation rates. Table 1 shows continuation rates, and Table 2 shows discontinuation rates for qualified centers.

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Table 1

Continuation rate/100 women by Kaplan-Meier estimates	
Time point (Year)	Rate (95%CI)
1	78 (77-81)
2	66(63-67)
3	58(55-61)
4	51(49-54)
5	47(44-50)

Table 2

Discontinuation rate/100 women by Kaplan-Meier at 5 years	
Reason	Rate (95% CI)
Hormonal reasons*	13.40 (11.0-15.79)
Planning pregnancy	13.33 (10.94-15.73)
Other medical reasons	11.30 (9.10-13.49)
Bleeding problems	10.05 (7.97-12.12)
Other personal(includes lost to follow-up)**	7.88 (5.90-9.85)
Expulsion	6.67 (5.07-8.28)
Pain	4.29 (2.82-5.75)
Amenorrhea	1.99 (1.01-2.98)
PID	1.22 (.53-1.91)
Other discontinuations	1.07 (.26-1.88)

*"Hormonal" includes skin problems, weight change, nausea, headache, mood changes, and breast tenderness.

**In the original study, 6.3% of the levonorgestrel IUD group were lost to follow-up at 60 months. That includes women from both qualified and unqualified centers.

Reviewer comments:

The pregnancy rate and continuation rates compare favorably to published rates for other reversible methods of contraception, including the ParaGard T 380A IUD. Unlike the ParaGard T 380A IUD, there are discontinuations for hormonal reasons and amenorrhea. Despite this, however, the overall rate of discontinuation is comparable between both IUDs.

3.10 Safety analysis

This section summarizes adverse events to evaluate the safety of the levonorgestrel IUD. First, the data from the reanalysis of qualified studies is presented. Then, selected data from the original study comparing the levonorgestrel IUD to the copper IUD is summarized.

3.10.1 Serious adverse events

There were no deaths.

Investigators detected 127 serious adverse events, summarized in Table 3 below.

Table 3

Serious Adverse Reactions among 1110 women in qualified sites	
Type	No.
Genital infections	16
Cervical dysplasia	9
Ovarian cyst	5
Abdominal pain	5
Cervical cancer (one invasive)	4
Breast cancer	3
Myoma	2
Myocardial infarction	1
Other	82

The report includes narrative summaries of the serious adverse events that support Table 3. The investigators and the sponsor did not consider the myomas, cervical dysplasias, cervical cancer, breast cancer, myocardial infarction or "other" events to be IUD-related. The breast cancer incidence in the study is within the expected range for breast cancer incidence in Finland in women ages 24–45. There was one case of invasive cervical cancer. There were no reports of serious liver toxicity. The 82 "other" SAEs consist of diverse events that were believed to have no apparent relationship to the levonorgestrel IUD, such as incontinence surgery, orthopedic surgery, hepatitis B infection, varicose vein surgery, etc.

The myocardial infarction occurred in a 42 year old women who had used the levonorgestrel IUD for 6 years when she was hospitalized for an acute anteroseptal myocardial infarction. She had been diagnosed with hypertension 3 years before entry into the study, and was under treatment at the time of entry. Admission blood pressure was 140/90 mm Hg. She was ultimately discharged from the hospital with the IUD in place.

The cervical cancer occurred in a 34 year old women who had used the levonorgestrel IUD for 33 months. She had normal PAP smears in 1983(baseline), 1984 and 1985. However, she complained of a brownish discharge at all of her routine visits. In 1986, a visible lesion was detected on the cervix on pelvic exam. Biopsy revealed squamous cervical cancer. She received radiation and had a total abdominal hysterectomy and salpingo-oophorectomy. She was referred to a gynecologic oncologist and there is no further information on the outcome.

Reviewer's comments:

Given that cervical dysplasia is not an uncommon finding among sexually active women and that the false-negative rate for a single PAP test (e.g., the cytology result at screening) is 10-25%, the finding of cervical dysplasia developing in 9 women during the course of the study probably does not suggest any significant effect of Mirena use on cervical cytology.

In the original study, cervical dysplasia rates were not statistically significantly different between Nova T users and users of Mirena. A single case of cervical cancer does not suggest a Mirena effect, as cervical cancer can occur in this age group. The annual incidence of cervical cancer in Finland was 3 per 100,000 among women aged 30-34 years (Muir, et al. Cancer incidence in Five Continents, Vol. V. International Agency for Research on Cancer, Publication no 88, Lyon 1987)

3.10.2 Frequent adverse events

98.6% of patients reported any adverse events (AEs). The most common adverse event was menstrual bleeding disorder, with 35.3% reporting intermenstrual bleeding, 27% reporting amenorrhea, and 16% reporting menorrhagia. Other common adverse events were abdominal pain (31%), leukorrhea (21%), headache (22%), acne (15%), depression (15%) breast pain (13%) and vaginitis (13%). Anemia was reported in 2%.

The most common adverse events leading to discontinuation of the IUD are summarized in Table 2.

In the original study, removal rates for menstrual cycle disturbances were about the same with both IUDs, with more removals for amenorrhea in the levonorgestrel IUD group and more for menorrhagia in the copper group. The overall rate of amenorrhea for the levonorgestrel IUD was 3 times greater than the removal rate for amenorrhea, suggesting that some women were not troubled by amenorrhea.

Also in the original study, the occurrence of PID was significantly lower with levonorgestrel IUD compared to the copper IUD. The 5 year gross removal rates for PID were 2.2 per 100 in the Nova T group and 0.8 per 100 in the levonorgestrel IUD group (p<0.01). The overall rate of PID is in agreement with rates published for reproductive

age women in 1980 in industrialized countries (1-1.3 per 100 women per year, *Am J Obstet Gynecol* 1980; 138:880-92).

Physicians reported that 16% of insertions were difficult. Women reported severe pain with 3% of the insertions, and moderate pain with 21% of the insertions. Physicians were unable to insert the levonorgestrel IUD in 1% of the women.

3.10.3 Changes in lab values

The mean hemoglobin (qualified +unqualified centers) rose from 135.8/l at baseline to 136.2g/l at 5 years. The mean hemoglobin for qualified centers rose from 133.9 to 135.7g/l at 5 years. All of these changes were statistically significant. However the clinical significance of these changes is unclear. In addition, more than half of the patients had discontinued by 5 years, including 10% for bleeding problems, and were therefore not included in the analysis at 5 years. It is worth noting however that in the original study upon which the reanalysis was based, the levonorgestrel IUD showed a net increase in hemoglobin and the copper showed a net decrease at all time points. For example, the respective mean changes at 5 years were +1.6g/l and –2.6g/l (p<0.04).

There was no significant difference in the incidence of cervical dysplasias between the levonorgestrel IUD group and the copper IUD group in the original study.

3.10.4 Changes in physical exam

Mean systolic and diastolic blood pressures dropped from 119.6mm Hg to 117.4mm Hg and 76.2 mm Hg to 73.9 mm Hg respectively at 5 years. Mean weight increased by 2.3 kg in 5 years. Eight percent of women reported weight increase as an adverse event. The changes in blood pressure and weight were statistically significant.

Reviewer's comments:

Many more women report menstrual abnormalities than discontinue the device for this reason. Patient counseling about likely menstrual changes will be important for successful use of the levonorgestrel IUD.

Although it is reassuring that the levonorgestrel IUD compares favorably to a copper IUD in the original study, the copper IUD used in the original study is not approved in the USA.

In the original study on which the reanalysis was based, the changes in blood pressure and weight were no different between the 2 IUDs suggesting that these changes were not a levonorgestrel effect.

4.0 STUDY B078

Five-year clinical performance of the new formulation of the levonorgestrel IUD and comparison of serum levonorgestrel concentrations of the new and original formulation

4.1 Objectives:

The first objective of this study was to evaluate the clinical performance of the levonorgestrel IUD with a reformulated steroid reservoir. The primary endpoints were pregnancy rates, continuation rates, discontinuation rates, and adverse events.

The second objective was to compare serum levonorgestrel concentrations between this new formulation and the original formulation used in Study AY99 (Section 3). The reformulation involved a change in the elastomer used in the steroid reservoir because the manufacturer stopped making the original elastomer.

4.2 Design

The study was an open, two center, phase 3 study of 390 levonorgestrel IUD users followed for up to 5 years. Fifty patients received the original levonorgestrel IUD containing ⁓mg of levonorgestrel and 340 patients received the new levonorgestrel IUD containing 52 mg of levonorgestrel. One hundred seventy-one patients completed 5 years, 150 with the new IUD and 21 with the original IUD. The original IUD containing ⁓ mg of levonorgestrel was the same device used in the AY99 study reviewed in section 3. Both study centers were in Finland. Recruitment began in 1990 and the study ended in 1996. Investigators did not do routine pregnancy testing, relying instead on patient history and a pelvic exam at each visit. However, the protocol suggested urine pregnancy testing if menses were 2 or more weeks late. If the pregnancy test was negative and 6 more weeks of amenorrhea ensued, another pregnancy test was recommended. If amenorrhea persisted, pregnancy testing was recommended when clinically indicated. Patients kept daily bleeding diaries for internal clinic use only. Visits were before insertion, at 3, 6, and 12 months, and annually thereafter. The only routine lab tests were cervical smears (done at 3 and 12 months, then annually thereafter) and serum levonorgestrel levels (done at 3,6,and 12 months, then annually thereafter).

4.3 Study population

There were no clinically important differences between the two groups. Mean age was 32.5 years. 77% had previously used IUDs.

4.4 Inclusion and exclusion criteria

Inclusion Criteria:

- *Subjects were informed of the purposes of the study. Written informed consent was obtained*
- Willing ess to rely solely on the levonorgestrel IUD for contraception
- Willingness to return to the clinic for regularly scheduled evaluations and to be available for regular follow-up
- Willingness to accept induced abortion in case of accidental pregnancy
- Insertion of the levonorgestrel IUD within 7 days of onset of menstruation
- 18-38 years old
- Regularly exposed to the risk of pregnancy
- At least one previous pregnancy. Nulliparous women were accepted if they had had one or more pregnancies.
- Menstruation after last pregnancy

Exclusion criteria:

- History or current clinical evidence of endocarditis
- History of cancer of any kind
- Pelvic inflammatory disease or salpingitis during the last 12 months
- Acute cervicitis or vaginitis
- History of ectopic pregnancy
- Persistent abnormal genital bleeding
- Galactorrhea
- Severe hirsutism
- Jaundice
- Severe varicosities
- Mental illness, depression
- Congenital or other abnormality of uterus
- Currently pregnant or breast feeding
- Use of injectable steroid hormones for contraception during 12 preceding months
- Drug treatment for epilepsy

4.5 Screening period

At screening the women had a general physical exam, a pelvic exam and completed paperwork. The pelvic exam was repeated at 3 months and annually. A PAP smear was done within 3 months of admission and annually thereafter.

4.6 Treatment period

A serum levonorgestrel was done at 3, 6, and 12 months, and annually thereafter. A general exam was done at each visit. Women kept menstrual diaries for clinic use only. They were questioned about their general health at each visit.

4.7 Statistical procedures

Life-table analysis using the Potter method was used for pregnancy, discontinuation and continuation rates. The log-rank-chi-square method was applied in evaluating the significance of differences between groups.

4.8 Withdrawals and compliance

Two women were lost to follow-up and 7 women withdrew from the study because they moved away. Discontinuation rates with reasons are included in the efficacy analysis since this was an efficacy endpoint in the study. Ten study numbers were not used. Of these, 5 were unsuccessful first attempts at insertion but the second attempt was successful and these women continued in the study with the number of the next IUD. One subject refused insertion after being assigned a numbered IUD. Two IUD's became unusable. One subject was excluded from the study because her first IUD was noted to be partially expelled 4 days after insertion, and a second IUD was inserted. This was against the study protocol. The first expulsion was documented as the reason for termination. One subject was excluded because she had abnormal bleeding and was not in the phase of the menstrual cycle required for insertion.

4.9 Efficacy analysis

The efficacy parameters were pregnancy rate, continuation rates, discontinuation rates, and serum levonorgestrel concentrations.

There were 3 pregnancies, all using the new prototype. Two of the pregnancies were ectopic, and I was presumed to be ectopic on clinical grounds but surgical intervention was not needed. The women were 25, 32 and 36 years old and had used their IUDs for 43, 5, and 44 months, respectively. For women who were 35 or younger at the start of the study, and based on 3164 28-day cycles, the first year Pearl index was 0.38 pregnancies per 100 women-years for the new prototype.

The 5-year cumulative continuation rate was 56% for the new levonorgestrel IUD and 58% for the original levonorgestrel IUD. The discontinuation rates were 44% and 42%, respectively. The differences in continuation and discontinuation rates were not statistically significant. Table 4 presents the reasons for discontinuation.

Table 4

5-year termination rates in percents for new IUD	
Reason	%
Planning Pregnancy	12
Hormonal	10
Bleeding problems	7
Pain	7
Medical	7
Expulsion	3
Personal	3
PID	2
Other removals	2
Pregnancy	1
Amenorrhea	1
Lost to follow-up	1

"Medical" included 3 women with adnexal problems, including 2 who had unilateral salpingo-oophorectomies. One of these women had a ruptured hemorrhagic cyst and the reason for salpino-oophorectomy in the other woman was not specified. The third woman had her IUD removed because of a cyst but did not require surgery.

There was a small but significant difference in serum levonorgestrel concentration in the first 3 years between the 2 IUDs, with consistently higher serum concentrations in women with the new prototype. See Table 5 below. There was no significant difference in AUC $_{(3-60months)}$. One subject with the new IUD had unusually high levonorgestrel concentrations in the first 2 years of the study (——— and ——— g/ml) that returned to the expected level by 3 years. She continued with the IUD to the end of the study.

Table 5

Median serum levonorgestrel in pg/ml (25-75 percentile ranges)		
Time(months)	New IUD	Original IUD
3	195(139-249)	144(120-194)
6	185(134-224)	153(122-178)
12	177(126-202)	133(96-142)
24	158(121-192)	141(126-173)
36	139(106-143)	114(103-127)
48	132(92-131)	126((104-135)
60	142(116-185)	129(101-175)

Reviewer's comments:

The high number of women who had previously used an IUD for contraception in both of the previous studies may favorably bias the continuatio:. rates. These high continuation rates may not be reproducible in a population without prior experience with an IUD.

The one patient with unusually high levonorgestrel levels does not raise a safety concern because the high levels in the patient are still considerably lower than the levonorgestrel levels seen with oral contraceptives containing levonorgestrel.

All pregnancies in the present study were ectopic, giving a Pearl index of 0.38 ectopic pregnancies per 100 woman-years. The study report quotes a Pearl index for ectopic pregnancies among sexually active women using no contraception of 1.2 to 1.6 per 100 woman-years (Lindblom B, Thorburn J. Spirialgraviditet. Lakartidningen 1988; 11:923-4), and therefore concludes that Mirena reduced the overall occurrence of ectopic pregnancy. However, the study report does not provide the 95% confidence interval around either Pearl index. In addition, women at increased risk for ectopic pregnancy (i.e. women with a history of ectopic pregnancy or a recent history of PID) were excluded from the study. Therefore, it cannot be concluded that Mirena reduces the risk of ectopic pregnancy from the data presented.

4.10 Safety analysis

4.10.1 Serious adverse events

There were no deaths.

There were 31 serious adverse events. Five women were hospitalized for PID, and a sixth woman was hospitalized for possible PID. Three women had surgery for ovarian cysts. There was one breast cancer, one cervical dysplasia, one suspected necrotic myoma and one case of depression. The remaining hospitalizations included a variety of problems, such as goiter surgery, surgery for bursitis, and disc surgery, and seemed unlikely to be related to IUD use.

4.10.2 Frequent adverse events

Ninety-eight percent of women reported any adverse event (not necessarily drug-related) in five years, the most common being headache (46%), abdominal pain (45%), menstrual disorder (41%), leukorrhea (22%), back pain (21%), and ovarian cyst (20%).

4.10.3 Changes in lab values

PAP smears were taken at 3 months, 12 months and annually, but not at baseline. Eight women had class 3 PAP smears and one woman had a class 4 PAP smear. At the 3 month evaluation, 85.55% had class 1 PAPs, 13.86% had class 2 PAPs, and 0.59% had class 3 PAPs (N=339). By 60 months, the corresponding numbers were 86.44%, 12.99% and 0.56%(N=205).

4.10.4 Changes in physical exam

Mean systolic and diastolic blood pressures increased significantly with time. The mean systolic blood pressure increased from 119.1 to 122.8 mm Hg from 0 to 60 months. The mean diastolic blood pressure increased from 74.4 to 80.3 mm Hg from 0 to 60 months. Both IUDs showed a statistically significant increase.

Reviewer's comments:

Since there is no non-IUD control group, it is difficult to assess the significance of adverse reactions. PID and ovarian cysts are two adverse reactions that might be more frequent in the levonorgestrel IUD users, and are discussed in the following paragraphs.

3 women had surgery for ovarian cysts in 1446 woman-years. For comparison, the reported annual incidence of ovarian cyst requiring hospitalization in the US for the years 1988-1990 was 327/100,000 or roughly 3 per 1000 per year.

There were a total of 9 diagnoses of PID in 1446 woman-years or 6.22 per 1000 woman-years. Six of these cases required hospitalization and were listed as SAEs. Three of the 9 occurred in the first month of IUD use. The remaining 6 cases occurred at 3,5,9,10,32, and 37 months of use. The pattern of an increased rate of PID shortly after IUD insertion has been previously described in a Lancet article in 1992. In this article, investigators used the World Health Organization's IUD clinical trial data to look at 51,399 woman years of IUD use. They found a risk of 9.7 per 1000 woman-years in the first 20 days after insertion compared to 1.4 per 1000 woman-years later than 20 days after insertion. 1552 of the 51,399 woman- years reported the use of the levonorgestrel IUD. The rates of PID in Lancet article were not significantly different with different IUDs.

The incidence of cervical dysplasia does not appear to rise from 3 months to 60 months. Since baseline PAP smears were not done the incidence of cervical dysplasia before Mirena use cannot be compared to the incidence of cervical dysplasia after use. However, given that cervical dysplasia is not an uncommon finding among sexually active women, the finding of 8 class 3 PAPs and 1 class 4 PAP among 390 women exposed to Mirena does not suggest any significant effect of Mirena on cervical cytology.

5.0 STUDY AV97

Comparison of levonorgestrel IUD with a birth control pill

5.1 Objectives

The objective of the study was to compare the clinical performance of the levonorgestrel IUD containing 52 mg of levonorgestrel with a desogestrel/ethinylestradiol birth control pill in young nulliparous women.

5.2 Design

The study was a one-year, open, prospective, randomized, parallel group study in two centers, one in Finland and one in Sweden. Group A received the 52-mg levonorgestrel IUD releasing 20 ug/day. Group B received a pill containing 150-ug desogestrel and 30 ug ethinyl estradiol. The pill was taken for 21 days followed by 7 days of placebo. The women were followed every three months for one year. Women kept bleeding diaries. Efficacy parameters were continuation rates, reasons for termination, pregnancy rates and insertion difficulties. Safety parameters were adverse event reports, bleeding patterns and exam findings including PAP smears, blood pressure and weight. There was no routine pregnancy testing, either at each visit or upon termination from the study. However, in the case of premature termination, the evaluation (including pelvic exam) that was planned for the 12-month visit was performed at the time of termination, if possible.

5.3 Study population

Two hundred subjects were randomized into the two treatment groups, 99 in the levonorgestrel IUD group and 101 in the pill group. Women were enrolled from 1993 to 1996.

There were no important differences in the following baseline characteristics of the two groups: mean age (22 years), mean height (167 cm), usual length of cycle (29 days) or duration of flow (5days). All patients except one were Caucasians. The women were between 18 and 25 years old.

5.4 Inclusion and exclusion criteria

Inclusion criteria:

- Written informed consent has been obtained
- Nulliparous women aged 18 to 25 in good general health
- Regular menses (every 24-35 days)
- Need for contraception for at least one year
- Normal uterine size (cavity 6-10 cm long)
- Normal cervical smear no more than 6 months old

- Body mass index less than 32
- Willingness to accept randomization either to the levonorgestrel IUD or to the birth control pill
- Willingness to return to the clinic for scheduled examinations and to complete bleeding diary

Exclusion criteria:

- Known or suspected pregnancy
- Uterine abnormalities distorting the uterine cavity or cervical canal
- Genital malignancy or breast carcinoma
- Current genital infection
- History of pelvic inflammatory disease
- History of ectopic pregnancy
- Acute liver disease or liver tumor
- Hypertension that requires treatment
- Active thrombophlebitis or thromboembolic disorder
- Diabetes
- Porphyria
- Systemic lupus erythematosis
- Major coagulation disorders
- Allergy to contraceptive steroids
- Treatment with enzyme inducing drugs e.g. barbiturates, phenytoin, carbamazepine, rifampicin or griseofulvin
- Use of injectable steroid hormone for contraception during 6 months preceding entry
- Use of anti coagulants concomitantly or during 2 months preceding entry
- Participation in another clinical drug study during the last 2 months preceding entry

5.5 Screening period

At screening investigators obtained consent, tested for chlamydia and obtained a cervical smear if more than 6 months had elapsed since the last smear.

5.6 Treatment period

Subsequent visits were at 0, 3, 6, 9, and 12 months. A general history and physical exam were done at entry. Investigators checked blood pressure and weight at every visit, and performed a gynecological exam at entry, 3 months, and 12 months. They collected bleeding diaries, recorded adverse events, and recorded concomitant treatment at 3, 6, 9, and 12 months. Women completed questionnaires at 0, 6, and 12 months.

5.7 Statistical procedures

Rates of pregnancy, continuation and discontinuation were calculated using Kapla. Meier estimates. A chi-square log-rank test was applied to group differences. Menstrual bleeding was analyzed using the Menstrual Diary System (MDS) developed by the World Health Organization (WHO).

5.8 Withdrawals and compliance

Of the original 200 randomized women, 94 received levonorgestrel IUD treatment and 99 received pill treatment. Five did not start treatment in the levonorgestrel IUD group and 2 did not start treatment in the pill group. Of the 5 who did not start treatment in the levonorgestrel IUD group, 3 were excluded because of positive culture results, one because her uterus was too small and one never came in for the insertion.

75 of 94 (80%) women completed 12 months of levonorgestrel IUD treatment and 72 of 99 women (73%) completed 12 months of pill treatment. Three women were lost to follow-up, 1 in the levonorgestrel IUD group and 2 in the pill group.

There were 71 minor protocol violations mostly involving forgotten or incorrectly taken pills.

5.9 Efficacy analysis

Efficacy parameters were continuation rates, reasons for termination, pregnancy rates and insertion difficulties.

No pregnancies were identified in either group. However, pregnancy testing was not done routinely, either during scheduled study visits or at study termination.

Ninety-two of 94 insertion attempts were successful, and 85 % were assessed as easy by the investigators. Most women complained of some pain on insertion, with 28% reporting mild pain, 37% reporting moderate pain, 21% reporting severe pain, and 14% reporting no pain.

The continuation rates at 12 months were 80 % by Kaplan Meier estimate in the levonorgestrel IUD group and 73% by Kaplan-Meier estimate in the pill group. Ninety-five percent confidence intervals overlapped. However, in the pill group 6 women terminated the study because they moved whereas only 1 in the levonorgestrel IUD group moved. In addition, in the pill group 2 women terminated the study because they forgot to take 3 or more pills.

There was 1 IUD-specific termination because of expulsion. There were no perforations or PID cases. Investigators reported no difficulty with the IUD removals.

The Kaplan-Meier termination rate for pain at 12 months was 7% with the levonorgestrel IUD and 0% with the pill. It was the only clinically important reason for termination to show a statistically significant difference between the two groups.

Reviewer Comment:

Investigators felt that 85% of insertions were easy, but only 14% of patients reported no pain. 58% reported moderate or severe pain. Labeling must be clear that pain on insertion is likely.

5.10 Safety analysis

5.10.1 Serious adverse events

There were no deaths.

There were 5 serious, adverse events, 3 in the oral contraceptive group and 2 in the levonorgestrel IUD group. Only one of these could be related to treatment and it occurred in the levonorgestrel IUD group. The woman reported abdominal pain after insertion of the levonorgestrel IUD. She was treated for possible cystitis and endometritis as an outpatient but was ultimately hospitalized for 2 days about 2 months after insertion, the levonorgestrel IUD was removed, she was treated with antibiotics and the pain resolved. The investigator felt that the pain was most likely secondary to either small uterine size or a partial expulsion.

5.10.2 Frequent adverse events

Adverse events leading to withdrawal from the study for the levonorgestrel IUD were

- Expulsion (1)
- Bleeding (2)
- Pain (6)
- hormonal complaints (4) (2 with acne, 1 with acne and weight change, and 1 with weight change only)
- unsuccessful insertions (2)
- personal (4) (2 did not like the idea of a foreign body, 1 moved and 1 was lost to follow-up)

5.10.3 Changes in lab values

There was no difference between groups in PAP smear results, either at baseline or at the end of the study. No other laboratory data was obtained.

5.10.4 Changes in physical exam

There was no statistically significant difference between treatment groups in systolic or diastolic blood pressure, at the baseline or at the end of the study. There was a small, but statistically significant drop in systolic blood pressure in the levonorgestrel IUD group at the end of the 12 months (from a mean of 120 mm at baseline to a mean of 117 mm Hg at the end of 12 months).

There was no significant difference in weight over time between the groups. For the levonorgestrel IUD group, the mean weight at baseline was 61.3 kg and the mean weight at 12 months was 62.4 kg. Corresponding figures for the pill group were 61.6 kg at baseline and 62.0 kg at 12 months.

In the levonorgestrel IUD group, two women developed cysts and one woman developed an adnexal mass. There were no adnexal disorders reported in the pill group.

From the symptom questionnaire, there was no difference between groups in depressed mood, edema or sexual parameters at 12 months. There were more skin and hair complaints in the levonorgestrel IUD group at 12 months.

The main findings from the menstrual questionnaire were a decrease in regular cycles from baseline to 12 months (89% to 27%) and an increase in the number of missed periods from baseline to 12 months (12% to 49%), both of which occurred in the levonorgestrel IUD group only. The change in proportion of women having regular cycles from baseline to 12 months was statistically significantly different between groups: in the pill group the percentage of women having regular cycles remained almost constant from baseline to 12 months (92.4% vs. 92.0%), whereas the percentage in the levonorgestrel IUD group decreased from baseline to 12 months (88.9% vs. 26.7%). The proportion of women reporting dysmenorrhea decreased from baseline to 12 months in the levonorgestrel IUD group (69.7% vs. 51.4%) and increased in the pill group (51.5% vs. 58.7%). These changes were statistically significantly different from each other.

For the bleeding diary analysis, 28-day cycles were combined into 84-day periods (three 28-day cycles). Four 84-day periods were evaluated. The bleeding/spotting/amenorrhea data from the first and the fourth 84-day periods is summarized in Table 6.

Table 6

Comparison of Bleeding between the IUD and Pill			
Bleeding data	Time period (84 days/period)	IUD	Pill
Median bleeding days	First	10	12.5
	Fourth	0	11
Median spotting days	First	20	6
	Fourth	7	4
Median number of bleeding episodes	First	3	4
	Fourth	0	3
Median number of spotting episodes	First	2	1
	Fourth	1	0
% with amenorrhea	First	1	0
	Fourth	21	1

Reviewers Comments:

This study does not give any information about future fertility in the nulliparous user of the levonorgestrel IUD. Although no cases met the study definition of PID, there was a case of abdominal pain requiring hospitalization, IUD removal and antibiotic treatment. Since pelvic infections and infertility have been historically associated with some IUDs, and since infertility is a serious issue for a nulliparous woman, it is prudent to avoid using the levonorgestrel IUD in nulliparous women, at least until data accrues to give some assurance that fertility is not impaired. There may be serious health or compliance reasons for choosing the levonorgestrel IUD in the nulliparous woman, but in general it should not be used as a first choice of contraception in this group.

The high incidence of menstrual irregularity and amenorrhea may limit this method of contraception in the general population. Clinicians need to be aware of these problems and women need to be counseled about these problems or it seems unlikely that high continuation rates seen in the study will be duplicated in the general population. This should be emphasized in the labeling.

There were 2 adnexal cysts and one adnexal enlargement reported in the levonorgestrel IUD group and none in the pill group. However, none of these cysts required surgical intervention. See also section 6.2 below.

6.0 Review of additional clinical data

This section reviews additional material submitted.

6.1 Additional studies on contraception

The sponsor submits 26 volumes containing 16 different study reports and publications on contraception. Some are controlled, some are uncontrolled, some have accessible case report forms and others do not. The studies are multinational and include Africa, China, South America, the United States and India in addition to a number of European countries.

In general, the findings support the findings in the pivotal studies. The pregnancy data show pregnancy rates of 0-2.5 pregnancies per 100 women. The study with 2.5 pregnancies per 100 women had a 30% loss to follow-up rate for levonorgestrel IUD users.

However, there are a few differences between these studies and the pivotal studies. There is a trend toward a higher incidence of ovarian cysts being reported in the more recent studies, perhaps reflecting the greater use of ultrasound to evaluate pelvic pain in recent times. The continuation rates are sometimes lower than in the pivotal studies. For example, 3-year continuation rates range from 39% to 75%, and 5-year continuation rates range from 33% to 53%. Possible explanations include differences in counseling or cultural differences in acceptability of spotting, amenorrhea or the IUD as a contraceptive method. One large study found a significant decrease in myoma incidence in levonorgestrel IUD users compared to copper IUD users. No new safety issues are identified.

6.2 Endometrial studies

The sponsor presents two studies of endometrial histology to show that no precancerous histologic changes occur in endometrium exposed to levonorgestrel-releasing IUD's. The endometrium shows atrophy, decidualized stroma and an inflammatory reaction. The histology reverts to normal patterns shortly after removal of the IUD.

One study evaluated endometrial histology in 12 women who had short-term exposure (1-4 months) to the levonorgestrel IUD. The study used 2 prototypes of Mirena, one releasing 20ug/day of levonorgestrel (8 women) and the other releasing ⎯⎯day of levonorgestrel (4 women).

The other study evaluated endometrial histology in 62 women who had long term exposure (7 years) to the levonorgestrel IUD. Twenty women used a 20ug/day prototype, 37 used a ⎯⎯ day prototype and 5 used unspecified other prototypes. Biopsies were done at removal and 1-6 months later.

Both studies showed atrophy and decidualization of the endometrium during IUD use.
The second study showed reversion to normal patterns on biopsies done 1-6 months after
IUD removal.

In summary, there were no adverse histologic findings after short or long term exposure
of the endometrium to the levonorgestrel IUD in the studies presented. Supportive studies
include 13 studies of endometrial histology with the levonorgestrel IUD used in
combination with estrogen for hormone replacement therapy. These are reviewed in
section 6.7.

6.3 Cervical studies

One study report and three published reports address cervical safety. In the study report
based on annual PAP smear data from 2758 women, investigators reported no difference
in the rate of dysplasia or cancer between women using Mirena (1821 women) and those
using a copper IUD (937 women). There were 46 subjects who developed abnormal
cervical cytology (Class III, IV or V), 13 in the copper IUD group and 33 in the Mirena
group. There was one invasive cervical cancer in the Mirena group (described in section
3.10.1). The differences were not statistically significant. The only other study to
address cervical cytology compared Norplant users to levonorgestrel IUD users and did
not show a significant difference in cytologic changes. However, this study had only 162
levonorgestrel IUD users, and the levonorgestrel IUD is described as a
levonorgestrel device.

Two cervical studies assessed microflora in levonorgestrel IUD users. There were no
significant differences seen among levonorgestrel IUD users (100 women), oral
contraceptive users (10 women) and copper IUD users (50 women).

6.4 Ovarian studies

Nine studies assessed the effect of the levonorgestrel IUD on ovulatory function. Because
the studies ranged over 19 years of levonorgestrel IUD development, the levonorgestrel
IUD was not identical to Mirena. However, in at least 5 of the studies, investigators used
similar 20 ug/day devices.

In general the levonorgestrel IUD did not suppress ovulation in most cycles. Investigators
saw an increase in ovulatory cycles over time from a low of 45% in the first year of use to
a high of 93% at 7 years. For example, a study of 10 women using a 20ug/day
levonorgestrel IUD showed that 13 of 29 cycles (45%) evaluated in the first year were
ovulatory. A study of 12 women using a 20ug/day levonorgestrel IUD showed that 15 of
17 cycles (88%) evaluated in year 4-5 were ovulatory. A study of 22 women using a
20ug/day levonorgestrel IUD showed that 26 of 28 cycles (93%) of the cycles in the
seventh year were ovulatory.

Reviewer's Comment: Ovulation suppression with the levonorgestrel IUD is inconsistent, decreases with time, and is therefore unlikely to be a major contributor to the contraceptive efficacy of Mirena.

6.5 Lactation studies

Three studies assessed the effect of the levonorgestrel IUD on lactation. The levonorgestrel IUD was inserted at 6 weeks postpartum in 2 of the studies and insertion time was not stated for the third.

Women using the levonorgestrel IUD had measurable amounts of levonorgestrel in their breast milk. The amount is less than that seen with Norplant, and plasma to milk ratio ranges from 100:15 to 100:25. In a small study of 14 lactating women and their infants (breast-feeding only), infant serum levonorgestrel concentration was about 7% of maternal serum levonorgestrel concentration. Infant growth at 1 year was no different between copper IUD users (N=40) and levonorgestrel IUD users (N=70). One study showed fewer women continuing to nurse at 75 days (44%) in levonorgestrel IUD users compared to copper IUD users (79%). The difference was statistically significant, and investigators felt it was possibly related to a decrease in milk production based on reasons women cited for discontinuing nursing.

6.5 Ovarian cysts

In a small study of 50 patients using a 20-ug/day levonorgestrel IUD in England, 6 women developed ovarian cysts between 3 and 7 cm. in diameter. Two of the 6 women needed laparoscopic intervention. The authors comment that other progestin-only contraceptive methods have been associated with cysts, and encourage expectant management.

In a study of the inserter, investigators did an ultrasound at 1.5 months after insertion and incidentally discovered 16 women with cysts larger than 3 cm in a group of 199 women. None required surgery.

One article by Barbosa, et al. describes cysts in 42% of 26 ovulatory cycles in women who had used a levonorgestrel IUD for more than seven years. These investigators used ultrasound every 1-2 days after day 8 in each cycle, and defined follicular cysts as persistent follicles greater than 30 mm in diameter. All cysts disappeared spontaneously by 45 days after diagnosis.

Reviewer's Comment: The incidence of ovarian cysts depends on the techniques used to look for them. Some of the patients with adverse event listed as pelvic pain in the pivotal studies may have had cysts if sonography had been used to evaluate them. There is precedence for cyst formation with progestins when they are used at levels that do not consistently inhibit ovulation, such as in the Norplant and the progestin-only

birth control pills. It is important to include the possibility of cyst formation in the label so that conservative management will be practiced whenever appropriate.

6.6

6.7 Endometrial protection in the perimenopausal and postmenopausal woman

The sponsor submits 45 volumes containing the results of ten controlled trials and three uncontrolled trials that support endometrial safety. Five of these studies provide lipid data as well. All of the trials use the levonorgestrel IUD in combination with different forms of estrogen-replacement therapy. The studies vary in design, in the estrogen used, and in the comparator progesterone used. They vary in length from 6 months to 2 years. Overall, however, approximately 540 women used a levonorgestrel IUD as the progesterone arm of their hormone replacement therapy. One woman had

simple cystic hyperplasia on endometrial biopsy after 6 months of levonorgestrel IUD use. Although her entry biopsy was negative, her endometrium measured 12 mm by ultrasound ... entry, raising the question of a preexisting condition. Additionally, the levonorgestrel IUD was described as "low-lying" on ultrasound, suggesting poor positioning as a factor.

Over 200 women had serum lipid testing in 5 of the studies. They were all taking various forms of estrogen as well, making it impossible to discern the effect of the levonorgestrel IUD alone on lipids. However, none of the 5 studies found clinically significant adverse effects on lipids when the levonorgestrel IUD was used with an estrogen.

Reviewers Comments:

The data in this part of the submission supports the data in section 6.2 and does not raise concerns about adverse endometrial effects from Mirena use.

The lipid data are confounded by the concomitant use of estrogen.

6.8 Return to fertility

Two publications address return to fertility in women who have the levonorgestrel IUD removed in order to become pregnant. Investigators studied about 250 patients. Pregnancy rates at 1 year range from 79-84%. These rates are comparable to general rates for women who are not using contraception. In one of the publications, the median time to pregnancy was 4 months for levonorgestrel IUD users (N=60). The data on time to pregnancy was not presented in the other publication.

6.9 Ease of insertion

The sponsor submits a study of ease of insertion in 199 women using a new inserter that is the same as the to-be-marketed inserter in all material respects. The new inserter was developed to overcome problems noted with the original inserter, including difficulties loading the IUD into the insertion tube, kinking of the insertion tube and problems in releasing the IUD from the insertion tube. The study enrolled women in three sites in Sweden and Finland from 1996 to 1997. Insertions were successful in all 199 women, though 7 women required 2 attempts. No medication was needed in 190 women. The clinicians were midwives, gynecologists and general practitioners. Only 1 woman complained of severe pain, though 54% experienced some pain.

Though the inserter is — nm in diameter, insertion difficulties are not commonly encountered by clinicians who provide routine family planning services.

7.0 Safety Update

Five periodic safety reports from Leiras Oy Drug Safety address the post marketing experience with Mirena. The reports cover 1992 through 1999 and include spontaneous reports, reports from the literature, and reports from ongoing clinical trials and observational studies. Leiras Oy estimates patient exposure from sales figures assuming a yearly discontinuation rate of 10% and five-year periods of use. This section summarizes the last safety report submitted at the time the NDA was submitted because it has the greatest estimated patient exposure and is likely therefore to be the most representative. This section also includes a discussion of total postmarketing experience with regard to pregnancy outcomes.

Reviewer's comment: Using a yearly discontinuation rate of 10% likely overestimates patient exposure since the discontinuation rate from the pivotal trials tends to be higher in the early years of Mirena use (see Table 1, section 3.9)

The last safety report submitted when the NDA was submitted covers the time between March 28, 1999 and September 27, 1999. Leiras Oy estimates that, at the end of September, 1999, there were about ˍˍˍˍˍˍ current users of Mirena worldwide. There were 2 reports of elevated liver enzymes, 4 reports of thrombophlebitis, 7 reports of hypertension, 5 reports of cancers and 58 reports of pregnancies. The cancers by type were 3 breast, 1 cervical and 1 teratoma. None of these events is more frequent than in the general population, but the extent of unreported cases is unknown. Of the 58 pregnancies, 21 were ectopic which is similar to the ratio seen in the pivotal studies.

Between 1992 and 1995 Leiras Oy received 4 spontaneous reports of severe group A streptococcal sepsis (GAS) from France and Sweden. In general severe pain occurred within hours of insertion, and the women involved were septic within days. Three of 4 women recovered, but the fourth was transferred after 6 weeks to a regional hospital in "improved condition" and was lost to follow-up.

Three of the four cases occurred in Sweden in 1994 and 1995 during a time when Sweden was experiencing a high incidence of severe GAS infections in general, with about 280 cases reported in 1994 and 230 cases between January and August 1995. Leiras estimates that these 3 cases of GAS in levonorgestrel IUD users came from a pool of about 150,000 Swedish levonorgestrel IUD users in 2.5 years. For comparison, in 1994-1995 the annual incidence of GAS in Sweden was 3.7 cases per 100,000 inhabitants.

In response to these reports, Leiras amended an ongoing postmarketing surveillance study (LE102-96502) to examine complications requiring hospitalization that may be related to insertion and use of the levonorgestrel IUD. Finnish hospital registries are being queried for such diagnoses in a cohort of approximately 26,000 users. The results are not yet available, but are expected to be available in 2001.

GAS information must be included on the label both to underscore the importance of good aseptic technique during insertion and to aid in early diagnosis in the rare event that GAS occurs.

GAS is known to cause serious invasive infection. It occurs at sites of injury, even minor injury, and may come from contact with asymptomatic carriers. For example, according to the CDC, since 1965 at least 15 postoperative or postpartum GAS outbreaks attributed to asymptomatic carriage in health-care workers have been reported. It is therefore not surprising that there are reports of GAS in levonorgestrel IUD users. This underscores the importance of good aseptic technique during insertion of the levonorgestrel IUD.

The public health significance of these 4 cases of GAS is unclear for several reasons. First, the real rate of GAS in levonorgestrel IUD users cannot be calculated from postmarketing reports. Secondly, we are missing control groups, for example, age-matched postpartum women. However, GAS is a potentially deadly infection that is clearly related to levonorgestrel IUD insertion in these 4 cases. GAS is not a risk of other contraceptive methods, such as birth control pills, though of course other methods have their unique risks as well. Therefore the label must address this rare but serious problem.

Experience with regard to pregnancy follows. There have been 35 infants reported with possible intrauterine exposure to the levonorgestrel IUD, including three infants with anomalies. One infant had an absent right pulmonary artery. The mother was also treated with carbimazole during the pregnancy for hyperthyroidism. Another infant had cystic hypoplastic kidneys and pulmonary hypoplasia, but was born to a mother who had a previous infant affected by renal agenesis and a previous second trimester loss. A third infant had partial fusion of the labia majora. The MedWatch form notes that 17-hydroxy progesterone levels were elevated.

—Reviewer's comments: Follow-up of exposed pregnancies is limited, but the 35 babies for whom birth outcomes are available do not suggest a pattern of birth defects. However, the number of reported pregnancies is too small to support meaningful conclusions about fetal risk.

Leiras performed postmarketing surveillance in Finland from 1990-1993. 26,630 women were enrolled at the time of insertion, and health care providers were asked to fill out a form if they removed the device. The extent of underreporting was unknown. However, 21 pregnancies were reported, 11 of which were ectopic. The study did not report pregnancy outcomes. The pregnancies occurred from 1 to 18 months after insertion, with no obvious clustering at any time period. Adverse events followed the general pattern of adverse events seen in the controlled trials without any unexpected events. A second, active surveillance was performed on the same group of women in 1996 with 75% of the women returning a signed survey. At that time, 108 pregnancies were reported, with 44

ectopic, 57 intrauterine and 7 unknown location. The study did not address infant outcome. The Pearl rate was 0.13 pregnancies per 100 woman-years in the first year of use. However, the Pearl rate includes women ages 18-61, with 31% of women in the study 39 or older.

Reviewer's Comments:

Leiras' large postmarketing surveillance did not raise any new safety concerns. The Pearl index cannot be compared to the Pearl index in the pivotal studies since so many women were 39 years old or older in the postmarketing surveillance study.

Berlex submitted a safety update during the NDA review that covered the period between September 28,1999 to March 27, 2000. No new safety issues were identified. Eighty-seven pregnancies were reported, of which 25 were ectopic.

8.0 Overview of Efficacy

The levonorgestrel IUD is an effective contraceptive method.

The total overall exposure to the levonorgestrel IUD was 92,129 woman-months in the three trials reviewed in sections 3, 4, and 5 above. Of those, 64,136 woman-months were in the qualified sites and 27,993 woman-months were in the nonqualified sites. A total of 877 women completed 5 years, 633 at the qualified sites.

The Pearl Index with a 95% confidence interval at 1 year is 0.19(0.02, 0.70) pregnancies per 100 woman-years. The Pearl Index with a 95% confidence interval at 5 years is 0.08(0.02, 0.23) pregnancies per 100 woman-years. The Pearl Index for ectopic pregnancies with a 95% confidence interval at 1 year is 0.097(0,0.54). These Pearl Indices are calculated from 1169 women from qualified sites who were between 18 and 35 years old at baseline in the two large contraception studies reviewed in sections 3 and 4.

The continuation rates in the 3 pivotal trials were 78/100 women at 1-year and 45/100 women at 5 years. These numbers are comparable to those estimated for other methods. For example 72 % of women continue on the birth control pill at 1 year and 78% continue with the Paragard IUD, according to *Contraceptive Technology.*

9.0 Overview of Safety

This section summarizes important safety results.

Total levonorgestrel IUD exposure in the 3 contraception trials reviewed in sections 3, 4, and 5 provide 5371 woman-years of data. The data from the unqualified centers in AY99 was excluded.

There were no deaths related to levonorgestrel IUD use.

This submission does not provide enough data to allow precise conclusions about the risk of PID in levonorgestrel IUD users compared to non-IUD users. However, there is support for the conclusion that the levonorgestrel IUD is no riskier than two different copper IUDs. The levonorgestrel IUD was not compared to either of the IUDs approved for use in the USA.

In the study on which the reanalysis study was based (see section 3), the 5-year discontinuation rate for PID was 0.8 for the levonorgestrel IUD and 2.2 for the Nova-T. The difference was statistically significant. In a large Population Council study, the 5-year cumulative rates of PID were 2.6 and 2.3 per 100 users for the levonorgestrel IUD and TCu380Ag devices, respectively. (The TCu380Ag is similar to, but not identical to, the ParaGard® T 380A IUD that is approved in the USA). There was no statistically significant difference between the devices.

Overall, there were sixty-five women in the 3 contraception trials diagnosed with PID/salpingitis, for a rate of 1 per 100 women-years. For comparison, 1980 annual incidence estimates of PID in modern industrialized countries were 1-1.3 per 100 women (*Am J Obstet Gynecol* 1980;138:880-92). In the 3 controlled contraception studies the discontinuation rates per 100 women by Kaplan-Meier were 0.93 at 1 year and 1.57 at 5 years. Overall, 2.7 % of women were diagnosed with PID/salpingitis.

PID was also assessed in 17 other clinical studies and 3 published studies. Because of different definitions and different ways of presenting the data, it is difficult to compare the studies. Overall, however, 1.5-3% of women were diagnosed with PID, which is comparable to the 2.7% from the 3 controlled contraception trials.

There have been 4 spontaneous postmarketing reports of severe group A streptococcal sepsis as of 1999(see section 7.0). In all 4 cases, symptoms started within hours of insertion. There were no cases in the three controlled contraception trials.

In some studies, ovarian cysts seem to occur with higher frequency than in the general population. However, most cysts are not clinically important. In addition, the reported incidence of ovarian cysts depends on how much effort is made to find them. For example, one study that was specifically designed to detect ovarian cysts showed cyst formation in 42% of 26 ovulatory cycles in women who had used the levonorgestrel IUD for more than 7 years. However, there were a total of 8 ovarian cysts listed as SAEs in the 3 controlled contraception trials reviewed in section 3,4, and 5. This reduces to 148/100,000 woman years. For comparison, the reported annual incidence of ovarian cyst requiring hospitalization in the US for the year 1988-1990 was 327/100,000.

The Pearl index for ectopic pregnancies in the qualified studies in women 35 and younger was 0.097 (95%C.I.=0.0, 0.544) per hundred women-years. The population Pearl index chosen by the sponsor as a historical control was 1.2-1.6 ectopic pregnancies per hundred women-years among sexually active women using no contraception (Lindblom B,

Thorburn J. Spiralgraviditet. *Lakartidningen* 11:923-4 1988). However, women at increased risk for ectopic pregnancy (i.e. women with a history of ectopic pregnancy or a recent history of PID) were excluded from the pivotal trials. In addition, as many as half of pregnancies that do occur are ectopic. For example, 5 of 10 pregnancies in the 2 large contraception trials and 65 of 108 pregnancies in the postmarketing reports and surveillance were ectopic. Labeling must include warnings that Mirena may not protect against ectopic pregnancy and ectopic must be ruled out if pregnancy occurs.

There were no perforations in 2339 attempted insertions.

There were no deep vein thromboses or pulmonary emboli in the 3 trials. There was one myocardial infarction (in report AY99) that occurred after 6 years of Mirena exposure in a 42-year-old woman with preexisting, treated hypertension.

Discontinuation for expulsions occurred in 97 of 2339 women in the 3 controlled studies. 70 of these expulsions occurred in the first year of use. The overall discontinuation rate for expulsion was 3.21 per 100 women at 1 year and 5.21 per 100 women at 5 years (cumulative). For comparison, discontinuation for expulsion for the ParaGard T 380 A IUD is 5.7 per 100 users in the first year of use.

Fetal safety data are limited. No pattern of birth defects emerges from 35 exposed pregnancies in which infant outcome data are available.

Endometrial biopsy on 74 women showed atrophy or decidualization of the endometrium in both short-term and long-term users of the levonorgestrel IUD, with no cases of atypical hyperplasia or endometrial cancer. One case of simple hyperplasia may have been pre-existing (see section 6.7).

Menstrual irregularity is common with levonorgestrel IUD use and affects continuation rates. Bleeding patterns were evaluated in 4 contraception studies and 3 published reports. The bleeding results in study AV97 (section 5.10.4) are typical of all these reports, and therefore are summarized as follows: The median number of bleeding days and spotting days in the first 84-day period were 10 bleeding days and 20 spotting days. However, this declined to 0 bleeding days and 7 spotting days in the fourth 84-day period. The percentage of women with amenorrhea in the first 84-day period was 1% but increased to 21% in the fourth 84-day period. Overall, in the three controlled contraception trials, the cumulative discontinuation rate by Kaplan-Meier for all bleeding irregularities was 16 per 100 women-years at 5 years.

The levonorgestrel IUD had no significant effect on weight or blood pressure over time when compared to a copper IUD or an oral contraceptive.

There was no difference in mean weight at baseline and other points up to 5 years between women using the levonorgestrel IUD and women using a copper IUD in study B075. In addition, there was no difference in mean weight at baseline and at 1 year

between women using the levonorgestrel IUD and women using a birth control pill in study AV97.

There was no difference in mean blood pressure (systolic or diastolic) at baseline and other time points between women using the levonorgestrel IUD and women using the copper IUD in study B075. In addition, there was no difference in systolic blood pressure at baseline between women using the levonorgestrel IUD and those using the birth control pill in Study AV97. However, there was a small, but statistically-significant drop in systolic blood pressure in the levonorgestrel IUD group at the end of 12 months.

In general mean hemoglobin levels tended to increase with time and there was a statistically significant effect in study AY99, from 135.8 to 136.2 g/L over 5 years. The clinical significance of a 0.4g/L rise in hemoglobin is unclear. In addition, only 47% of the women who started in the study were still in the study at 5 years and 10% had discontinued because of bleeding problems. The rise in hemoglobin may therefore be partly or wholly explained by the loss of women with low hemoglobin levels as the trial continued. However, in the comparative study B075, mean hemoglobin levels were the same at baseline for women using the levonorgestrel IUD and women using the copper IUD (Nova T), but were higher for all subsequent visits for the levonorgestrel IUD users compared to the copper IUD users. For example, the mean changes from baseline at 5 years were +1.6g/l for the levonorgestrel IUD and −2.6g/l for the copper IUD (p < 0.04).

The sponsor presents no data on lipids or glucose in women using the levonorgestrel IUD for birth control. The data on lipids and glucose comes from studies in women using the levonorgestrel IUD as the progestin part of a HRT regimen, and are thus confounded by the concomitant use of estrogen. However, systemic levonorgestrel levels are lower in levonorgestrel IUD users than in users of other levonorgestrel birth control products, and it is reasonable to expect that systemic effects will be the same or less with the levonorgestrel IUD.

The sponsor presents no data on bone density. However, there is literature support for no adverse effect on bone density from Norplant implants, which produce somewhat higher systemic levels of levonorgestrel.

Abnormal cervical cytology in levonorgestrel IUD users does not appear to be different from that seen in sexually active women (see section 2.4.2).

The incidence of breast cancer incidence in levonorgestrel IUD users in these studies is no higher than the expected incidence in women of reproductive age. There were 4 breast cancers in 5371 woman-years in the 3 controlled contraception trials, or 74/100,000 woman-years. The 4 women ranged in age from 36 to 44, and had used the levonorgestrel IUD from 3 to 6 years. For comparison, the incidence of breast cancer among women aged 35- 44 years in Finland between 1977-1981 varied between 40 and 74 per 100,000 women per year.

10.0 Final Conclusions and Recommendations

Mirena is an effective contraceptive device with a safety profile similar to other IUDs and hormonal methods of contraception. Approval is recommended based on the clinical review.

American women currently have 2 IUD choices, the ParaGard® T 380A IUD and the Progestasert®. The use of the Progestasert® is limited by its one-year duration of effectiveness, because many IUD risks are greatest around the time of insertion. Therefore, for practical purposes, the ParaGard® T 380A IUD, with a 10-year duration of effectiveness, is the only IUD currently available and used by American women.

Mirena offers an alternative to the ParaGard® T 380A IUD that may appeal to women with heavy menstrual flows. The typical user will be a multiparous woman desiring long-term contraception. As for all IUDs, the user must be at low risk for pelvic infection.

Women and their healthcare providers must consider the following potential adverse events when considering Mirena as a method of contraception:

- Amenorrhea. One in 5 Mirena users has amenorrhea at 1 year. For a woman with heavy menstrual flow, this may be a welcome effect. However, it may also cause distressing pregnancy fears or a missed diagnosis of pregnancy. A reasonable approach to the problem is pregnancy testing and examination when amenorrhea first occurs, and then as needed for changes in the menstrual pattern or symptoms of pregnancy. However, women and their doctors must know about this before insertion.

- Ovarian cysts. Delayed follicular atresia is a problem common to all current progestin-only methods of contraception. Women and their healthcare providers must know about this risk to avoid unnecessary surgery for simple, transient cysts.

- Systemic exposure to levonorgestrel. Systemic levels of levonorgestrel are lower for Mirena than any other currently available levonorgestrel-containing method. Even so, there is systemic exposure. Therefore, women who have any contraindication to levonorgestrel should not use this method.

- Fetal exposure to levonorgestrel. In the unlikely event of pregnancy with the levonorgestrel IUD in place, the fetus is exposed to high concentrations of levonorgestrel. Berlex has limited pregnancy outcome data. Because Mirena is so effective, data on human fetal effects are likely to remain limited.

In addition to recommending approval, it is further recommended that Berlex

- follow the usual post approval reporting requirements for both adverse event reports as well as further studies. In particular Berlex must submit the final report of study

LE102-96502 in 2001. This was a large postmarketing study of 26,000 users in Finland that evaluated, among other things, complications requiring hospitalization related to insertion.

- follow up adverse event reports related to pregnancy for as much outcome information as possible. Pregnancy reports must be followed up for birth defects, septic abortions, premature deliveries, and duration of the exposure to Mirena whenever this information can be obtained.

- provide a separate section in the periodic safety update reports for USA adverse event data and estimates of exposure to Mirena. IUDs are not widely used in the USA and it is possible that lack of experience will adversely affect the safety profile of Mirena. For example, perforations may be a greater problem in the USA than elsewhere.

11.0 Labeling

The labeling was edited extensively for consistency, clarity, and errors. Information on group A streptococcal sepsis was added, as well as a description of the small pregnancy series from postmarketing data. Discrepancies between the patient and physician inserts were corrected.

The sponsor included a comparison between their corporate core text (CCT) label and the proposed U.S. label, as well as comparisons between their CCT label and the labels from 14 countries. Most differences were minor. Six of the 14 countries list ———————— as a contraindication. In the proposed U.S. label, it was listed in the ——— section. Since there is no clear, statistically significant data ———— ——————————————————————————————— this ——— was removed from the label.

However, the following two contraindications were added:
        Carcinoma of the breast
        History of ectopic pregnancy

Breast cancer was added because it can be a progestin-stimulated disease.

The submitted label was inconsistent in its advice about ectopic pregnancy risk. The patient insert clearly stated that a woman with a history of ectopic pregnancy should not use Mirena, but the physician label was equivocal. It is recommended that ectopic history be a contraindication because Mirena may not be effective at preventing ectopic pregnancies, and because the pivotal trials excluded women with a history of ectopic pregnancy.
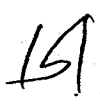
The patient information brochure was rewritten in a question-answer format to shorten and simplify the brochure submitted by Berlex.

12.0 Glossary

AE	adverse event
AUC	area under curve
CDC	Center for Disease Control
CRF	case report form
GAS	group A streptococcus
HRT	hormone replacement therapy
HCG	human chorionic gonadotropin
IND	investigational new drug
IUD	intrauterine system
MDS	menstrual diary system
NDA	new drug application
PAP	Papanicolaou smear
PID	pelvic inflammatory disease
PSUR	Periodic Safety Update Report
SAE	serious adverse event
WHO	World Health Organization

/s/ 4/5/2000

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/s/ ____, MD 12/5/00

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Cc: HFD-580/S.Allen/D.Shames/D.Hixon/J.Best/L.Furlong
Cc: NDA 21,225 Division File

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

See Medical Officer Review, Page 39, for Safety Update Review

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